REMARKS

Upon entry of the accompanying amendment, Claims 1-3, 5, 8, 9, and 12 are all the claims pending in the application. Claim 12 is withdrawn from consideration as directed to non-elected invention. Claim 1 has been amended to incorporate the feature of claim 4 and claim 4 is canceled, accordingly.

Therefore, no new matter has been introduced. Entry of the amendment and reconsideration of the application are respectfully requested.

Applicants thank the Examiner for withdrawing the rejection under 35 U.S.C. §112, second paragraph in view of the amendment filed on January 29, 2008.

Claim Rejection under 35 U.S.C. § 103

In the Advisory Action, the rejection of claims 1-5, 8, and 9 under 35 U.S.C. §103 is maintained. Claims 1-5, 8 and 9 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Braxton (US 5,766,897) ("Braxton") and Kay *et al.* (US 2002/0077294) ("Kay").

In the final Office Action dated October 29, 2007, Braxton is relied upon to teach a PEG-polypeptide dimeric complex (column 13 line 56) of the general formula R1-S-PEG-S-R2 where R1 and R2 may represent the same or different proteins. The Office asserts that Braxton teaches that human growth hormone (hGH) (Table IA and column 12 line 1) is a polypeptide that can be a part of the complex which would result in hGH-first PEG-hGH; and that PEG can be attached at particular residues (column 12 line 49). It is further asserted that Braxton teaches that the

residue could be naturally present in the protein or could be introduced by site-directed mutagenesis (column 13 line 64-66); that the PEG linker/moiety (i.e. first PEG) may be in the range of 0.2-20 kDa (column 12 line 50); and that a lysine residue is typically reacted with PEG (column 2 line 12).

The Office admits that Braxton does not expressly teach further pegylation of the PEG dimer with PEG of a different molecular weight, nor expressly teach the PEG groups such as those recited in claim 5 and 8 of the current invention.

The Office relied upon Kay to fill the gap. The Office asserts that Kay teaches polypeptide derivatives in which a protein is linked to a nonproteinaceous moiety (e.g. a polymer) in order to modify properties; and teaches PEG as an example of the polymer and its modification at the amino terminus of the protein. The Office further asserts that Kay teaches protein dimers via PEG crosslinkers; and the polymer (i.e. PEG) having a molecular weight of 2-100 kDa.

It appears to Applicants that the Office takes a position that one would be motivated by Braxton to obtain a polypeptide-first PEG-polypeptide dimeric protein (i.e. hGH-firstPEG-hGH) since Braxton teaches such a protein; and the pegylation of the dimer (hGH-PEG-hGH) would be desirable and result in secondPEG-hGH-firstPEG-hGH-secondPEG where the molecular weight of first PEG is 0.2-20 kDa and the molecular weight of the second PEG is 2-100 kDa.

Applicants respectfully traverse the rejection.

The currently claimed invention of claim 1 is directed to a [second PEG]-[polypeptide]-[first PEG]-[polypeptide]-[second PEG] complex, in which the first PEG molecule has a

molecular weight ranging from 2 kDa to 20 kDa and the second PEG molecule has a molecular weight ranging from 20 kDa to 40 kDa, and the molecular weight of the second PEG molecule is larger than that of the first PEG molecule.

The currently claimed PEG-polypeptide homodimer complex has a structure in which the specified parts of two molecules of a polypeptide are connected via the first PEG molecule having a molecular weight of 2 to 20 kDa, and wherein the respective polypeptide is modified with the second PEG molecule having a larger molecular weight of 20 to 40 kDa.

Neither of Braxton nor Kay, single or in combination, teaches all and every elements of the currently presented claim 1. Braxton merely discloses that the PEG molecule may have a molecular weight of 0.2 to 20 kDa. Kay merely teaches that the PEG molecule may have a molecular weight ranging from 2 kDa to 100 kDa. Braxton and Kay both fail to teach a first PEG molecule and a second PEG molecule, which each are coupled through a different linkage to a peptide molecule. Furthermore, they also fail to provide any suggestion or motivation to modify the PEG-polypeptide complex to reach the currently claimed invention, with reasonable expectation of success. That is, neither of Braxton nor Kay provides motivation to select or modify the first PEG molecule and the second PEG molecule, each having the specific range of molecular weights, wherein the molecular weight of the second PEG molecule is larger than that of the first PEG molecule.

In addition, the currently claimed invention shows unexpected effects. As Test Examples 5 and 6 of the present application show, the currently claimed complex shows reduced decrease in the biological activity thereof and increased *in vivo* stability of the polypeptides to prolong *in*

vivo activity of the peptides (*see* lines 14-21, page 2; and lines 13-14 and 19-21, page 4 of the present specification). *See*, also Table 4 and Fig. 3 of the present application.

Therefore, the subject invention defined in currently presented claims 1-3, 5, 8, and 9 is clearly patentable over Braxton and Kay, and it is respectfully requested that the rejection under 35 U.S.C. 103 be withdrawn.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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